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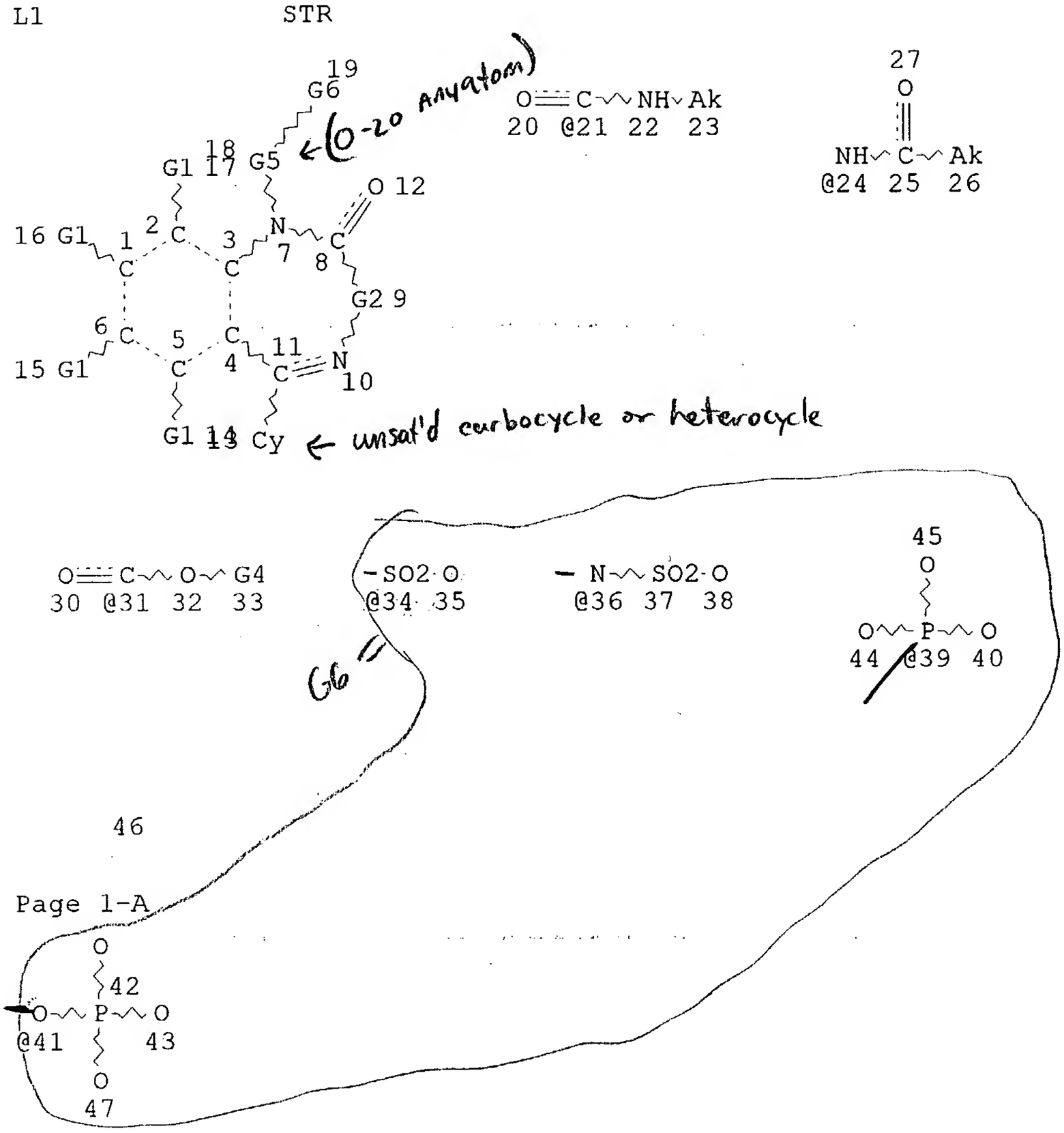
L1 STR



Considered 11/08/04 MEC

Page 2-A
VAR G1=H/X/NO2/NH2/21/24
VAR G2=CH2/28
VAR G3=AK/OH/31
VAR G4=H/AK
REP G5=(0-20) A
VAR G6=34/36/39/41
NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
GGCAT IS UNS AT 13
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 47

STEREO ATTRIBUTES: NONE

L3 4 SEA FILE=REGISTRY SSS FUL L1
L4 2 SEA FILE=HCAPLUS ABB=ON PLU=ON L3

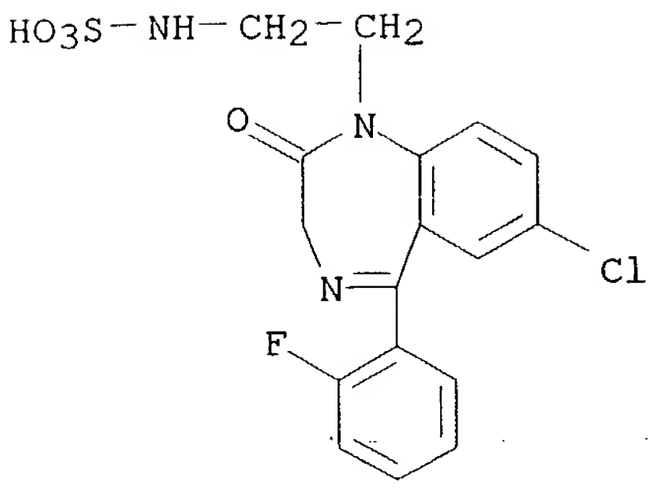
=> d l4 ibib abs hitstr 1-2

L4 ANSWER 1 OF 2 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:591434 HCAPLUS
DOCUMENT NUMBER: 139:143888
TITLE: Water-soluble derivatives of lipophilic drugs for use as standards for immunoassays of lipophilic drugs, and preparation thereof
INVENTOR(S): Li, Min; Wu, Robert S.; Tsai, Jane S. C.
PATENT ASSIGNEE(S): Roche Diagnostics GMBH, Germany; F. Hoffmann-La Roche AG
SOURCE: PCT Int. Appl., 46 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003062819	A2	20030731	WO 2003-EP655	20030123
WO 2003062819	A3	20040401		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003153096	A1	20030814	US 2002-57762	20020125
EP 1468295	A2	20041020	EP 2003-731624	20030123
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				

this applicn

PRIORITY APPLN. INFO.: US 2002-57762 A 20020125
WO 2003-EP655 W 20030123
OTHER SOURCE(S): MARPAT 139:143888
AB A water-soluble reference standard is useful for immunoassays of a lipophilic drugs.
The reference standard is a compound G(L)nY [G = lipophilic drug; L = linker (hetero)alkyl group containing 1-20 C; n = 0, 1; Y = water-solubilizing group, e.g. -SO3-, NRSO3-, P(=O)(OH)(O-), OP(=O)(OH)(O-); R = H, C1-10 alkyl]. Methods of preparing compds. of the invention are included.
IT **569660-00-0P**
RL: ANT (Analyte); ARU (Analytical role, unclassified); PRP (Properties); SPN (Synthetic preparation); ANST (Analytical study); PREP (Preparation)
(lipophilic drug water-soluble derivative preparation for immunoassay standard)
RN 569660-00-0 HCAPLUS
CN Sulfamic acid, [2-[7-chloro-5-(2-fluorophenyl)-2,3-dihydro-2-oxo-1H-1,4-benzodiazepin-1-yl]ethyl]- (9CI) (CA INDEX NAME)



RL: ARU (Analytical role, unclassified); ANST (Analytical study)
(lipophilic drug water-sol. deriv. prepn. for immunoassay std.

L4 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1970:55525 HCAPLUS
DOCUMENT NUMBER: 72:55525
TITLE: 7-Chloro-1-(2-hydroxyethyl)-5-(o-fluorophenyl)-1,3-dihydro-2H-1,4-benzodia zepin-2-one carboxylic acid esters
INVENTOR(S): Fryer, Rodney I.; Sternbach, Leo H.
PATENT ASSIGNEE(S): Hoffmann-La Roche, F., und Co., A.-G.
SOURCE: Ger. Offen., 44 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 1923139	A	19691120	DE 1969-1923139	19690507
DE 1923139	C2	19820415		
CH 568996	A	19751114	CH 1969-6315	19690425
CH 579058	A	19760831	CH 1971-15812	19690425
CH 579059	A	19760831	CH 1971-15813	19690425
CA 950455	A1	19740702	CA 1969-50258	19690501
GB 1208541	A	19701014	GB 1969-1208541	19690505
BE 732558	A	19691106	BE 1969-732558	19690506
AT 288404	B	19710310	AT 1969-4344	19690506
ES 366841	A1	19710401	ES 1969-366841	19690506
NO 123492	B	19711129	NO 1969-1865	19690506
DK 142456	B	19801103	DK 1969-2478	19690506
DK 142456	C	19810803		
NL 6906971	A	19691111	NL 1969-6971	19690507
NL 165176	B	19801015		
NL 165176	C	19810316		
SE 351647	B	19721204	SE 1969-6468	19690507
JP 48010479	B4	19730403	JP 1969-35117	19690507
DK 126201	B	19730618	DK 1971-4069	19710819
US 3819602	A	19740625	US 1971-186399	19711004
DK 143900	B	19811026	DK 1972-911	19720228
DK 143900	C	19820510		

JP 48035279 B4 19731026 JP 1972-111340 19721108
PRIORITY APPLN. INFO.: US 1968-727356 19680507
US 1969-806702 19690312
US 1968-806702 19680312
DK 1969-2478 19690506

GI For diagram(s), see printed CA Issue.

AB Title compds. were prepared as sedatives. Thus, to a solution of 10 g 7-chloro-5-(2-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one-HCl in 25 ml DMF was added a solution of 0.0415 mole NaOMe in 10.6 ml MeOH, and the mixture stirred 30 min at 20°, treated with 8.7 g 2-bromoethanol, and heated 2 hr at 80° to give 7-chloro-5-(2-f lurophenyl)-1-(2-hydroxyethyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one (I); HCl salt m. 194-6° (decomposition) (MeOH-Et2O). Alternatively, 1 g 7-chloro-5-(2-fluorophenyl)-3H-1,4-benzodiazepin-2(1H)-one in 15 ml DMF was treated with a solution of 0.9 ml 4.69N NaOMe, the mixture stirred 30 min, a solution of 0.45 g ethylene oxide in 5 ml DMF added, and the mixture stirred 2 hr at 20° and 1 hr at 60° to give I. A solution of 4 g I in 40 ml anhydrous pyridine was treated with 8.2 g 3,4,5-trimethoxybenzoyl chloride to give I 3,4,5-trimethoxybenzoate, m. 161-3° (MeOH, CH2Cl2, hexane). Other examples were given.

IT **26308-25-8P 26508-58-7P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)

RN 26308-25-8 HCAPLUS

CN 2H-1,4-Benzodiazepin-2-one, 7-chloro-5-(o-fluorophenyl)-1,3-dihydro-1-(2-hydroxyethyl)-, hydrogen sulfate (ester), compd. with triethylamine (1:1) (8CI) (CA INDEX NAME)

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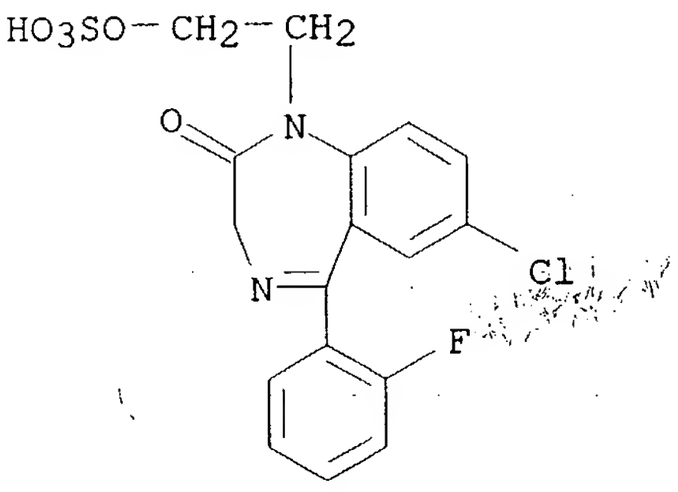
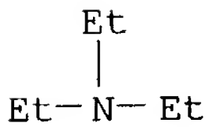
CRN 17617-58-2
CMF C17 H14 Cl F N2 O5 S

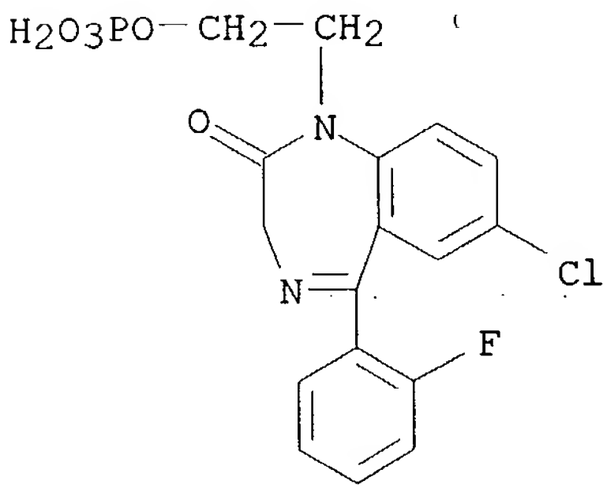


CM 2

CRN 121-44-8
CMF C6 H15 N

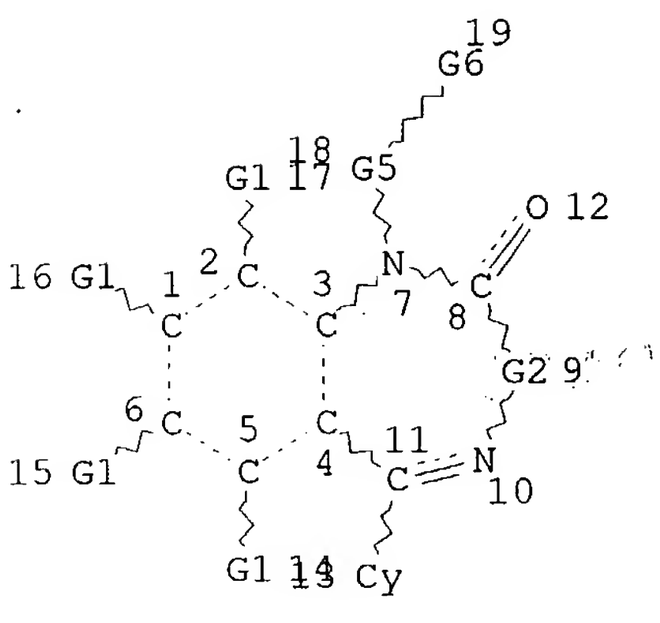


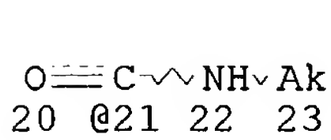
RN 26508-58-7 HCAPLUS
CN 2H-1,4-Benzodiazepin-2-one, 7-chloro-5-(o-fluorophenyl)-1,3-dihydro-1-(2-hydroxyethyl)-, dihydrogen phosphate (ester) diammonium salt (8CI) (CA INDEX NAME)

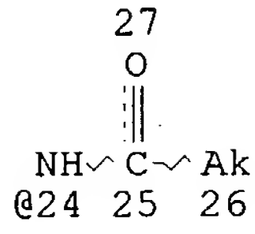


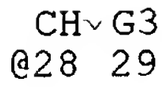
● 2 NH_3

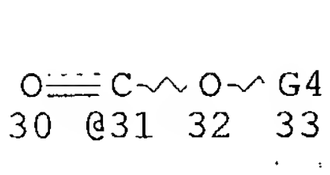
=> d que
L1 STR

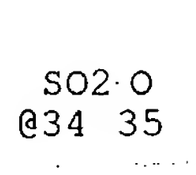


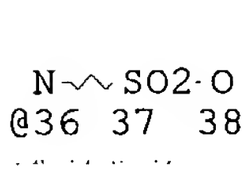


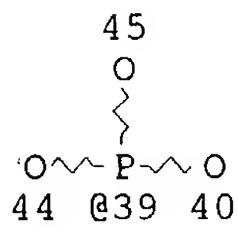












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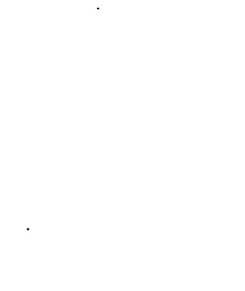
Page 1-A



Page 2-A
VAR G1=H/X/NO2/NH2/21/24
VAR G2=CH2/28
VAR G3=AK/OH/31
VAR G4=H/AK
REP G5=(0-20) A
VAR G6=34/36/39/41
NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
GGCAT IS UNS AT 13
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 47

STEREO ATTRIBUTES: NONE

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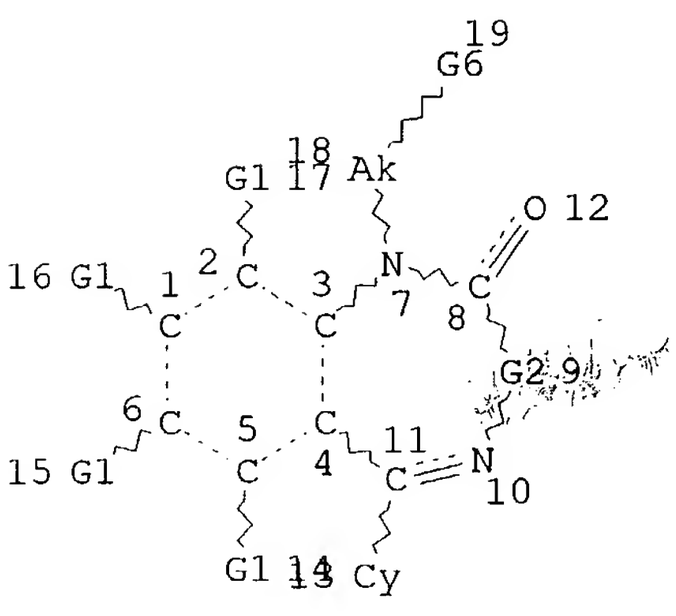
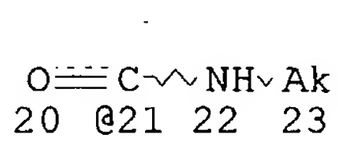
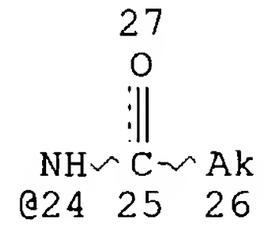
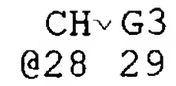
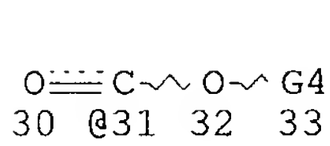
L4 2 SEA FILE=HCAPLUS ABB=ON PLU=ON L3
L12 STR

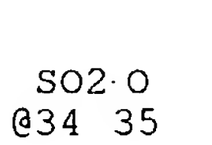


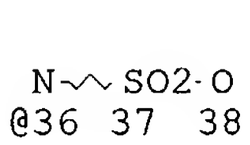


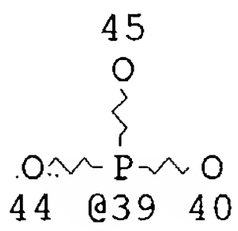












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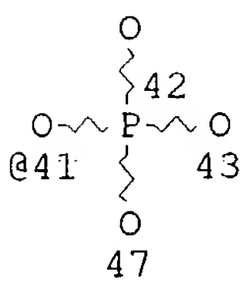
Page 1-A



Page 2-A
VAR G1=H/X/NO2/NH2/21/24
VAR G2=CH2/28
VAR G3=AK/OH/31
VAR G4=H/AK
VAR G6=34/36/39/41
NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
GGCAT IS UNS AT 13
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 47

STEREO ATTRIBUTES: NONE
L14 3 SEA FILE=MARPAT SSS FUL L12

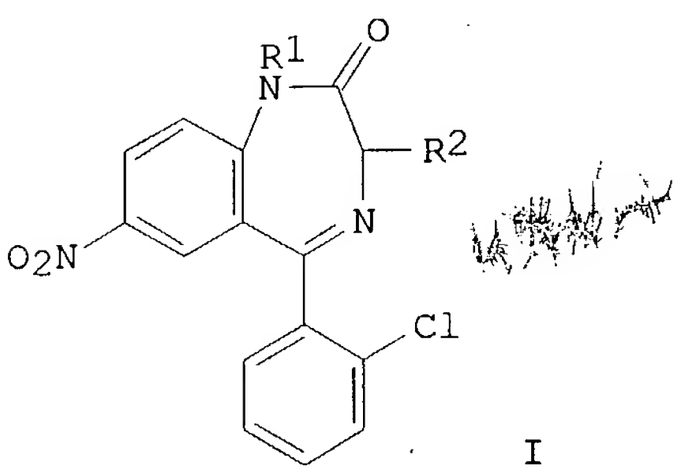
L15 2 SEA FILE=MARPAT ABB=ON PLU=ON L14 NOT L4

=> d l15 ibib abs qhit 1-2

L15 ANSWER 1 OF 2 MARPAT COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 118:101995 MARPAT
TITLE: Preparation of 1- or 3-substituted chlonazepam derivatives as haptens and antigens for immunoassay of chlonazepam
INVENTOR(S): Kanehiro, Masahiko; Akita, Tatsuo; Yajima, Ryuichi; Kumagai, Yasuyuki; Nakaya, Miho
PATENT ASSIGNEE(S): Dainabot Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 18 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 04202186	A2	19920722	JP 1990-330156	19901130

PRIORITY APPLN. INFO.: JP 1990-330156 19901130
GI

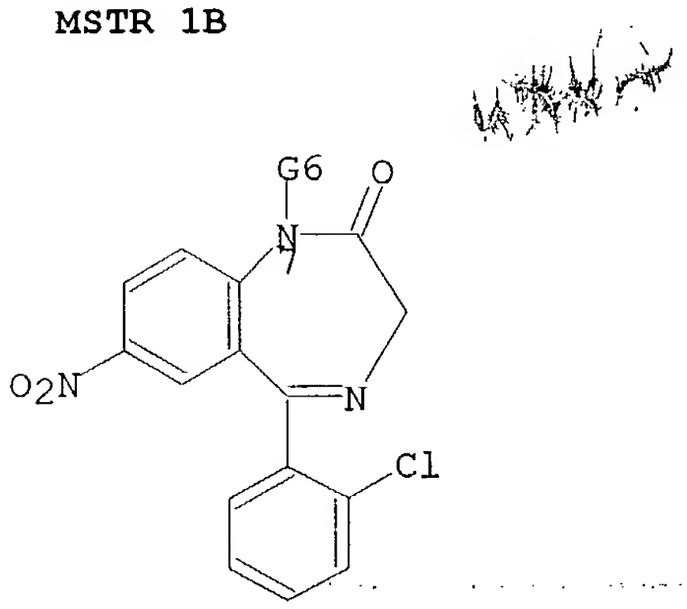


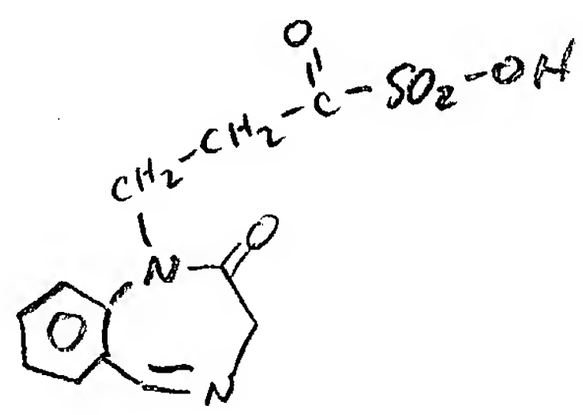
I

AB The title compds. [I; one of R1, R2 = H, the other = RZQ; R = C1-10 linkage group containing a hetero atom and a linear or branched chain containing ≤10 heteroatoms in which ≥2 of the hetero atoms are not directly bonded to each other; Z = CO, C:NH, NH, NMe, N:N, SO2, CH2; Q = H, HO, halo, acyloxy, N-succinylimidoxy, N-phthalimidoxy, alkoxy, (un)substituted PhO, N-imidazolyl, 1-benzotriazolyloxy, polyamino acid or its derivative, or other antigen carrier, labeled compound] are prepared as antigens for enzyme immunoassay, RIA, and fluorescence immunoassay of chlonazepam in the treatment plan using chlonazepam as an anticonvulsant. Preferred compds. are I (Q = bovine serum albumin, fluorescent substance, fluorescein, enzyme, radioactive material). Thus, 108 mg chlonazepam was stirred with MeONa in MeOH-DMF at room temperature, thereto 276 μL BrCH2CO2CMe3 was added, and the mixture was stirred overnight at room temperature to give 88% I (R1 = CH2CO2CMe3, R2 = H) which was treated with 50% CF3CO2H in CH2Cl2 to give 90% (R1 = CH2CO2H, R2 = H). This (37.4 mg) was

esterified with N-hydroxysuccinimide in the presence of DCC in DMF-dioxane to give an active ester solution which was reacted with aqueous solution of 110 mg bovine serum albumin adjusted to pH 8.5 with 0.1N NaOH while maintaining the same pH to give, after dialysis and freeze dry, antigen I (R1 = CH2CO2Q, Q = bovine serum albumin, R2 = H). Inoculation of mice with this antigen produced anti-chlonazepam monoclonal antibody which showed cross-reactivity 100, <0.1, and 20% to chlonazepam, metabolites 7-aminochlonazepam, and 3-hydroxychlonazepam, resp.

MSTR 1B





G1 = 74-7 126-24

$H_2C^{74}-CH_2-CH_2-C^{126}(O)$

G3 = SO2
G5 = OH
MPL: claim 1

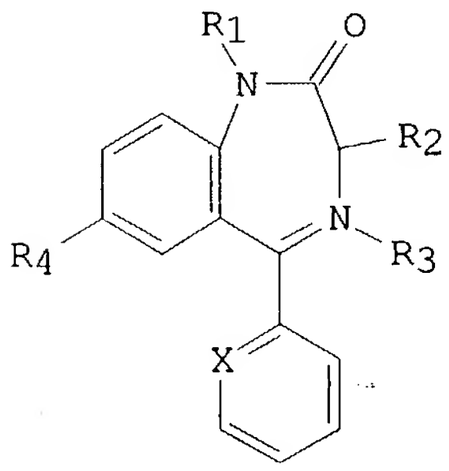
L15 ANSWER 2 OF 2 MARPAT COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 110:91693 MARPAT
TITLE: Benzodiazepines assay, tracers, immunogens and antibodies
INVENTOR(S): Wang, Nai Yi; Keegan, Candace Linda; Heiman, Daniel Fuelner; Flentge, Charles Arthur; Wang, Philip Pei
PATENT ASSIGNEE(S): Abbott Laboratories, USA
SOURCE: Eur. Pat. Appl., 25 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 264797	A2	19880427	EP 1987-114982	19871014
EP 264797	A3	19900207		
EP 264797	B1	19960110		
R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE				
AT 132974	E	19960115	AT 1987-114982	19871014

ES 2084577	T3	19960516	ES 1987-114982	19871014
AU 8779975	A1	19880428	AU 1987-79975	19871021
AU 604766	B2	19910103		
JP 63246666	A2	19881013	JP 1987-269158	19871023
JP 06060166	B4	19940810		
CA 1339439	A1	19970902	CA 1987-550168	19871023
AU 9169215	A1	19910711	AU 1991-69215	19910107
AU 643490	B2	19931118		

PRIORITY APPLN. INFO.: US 1986-922595 19861024
AU 1987-79975 19871021

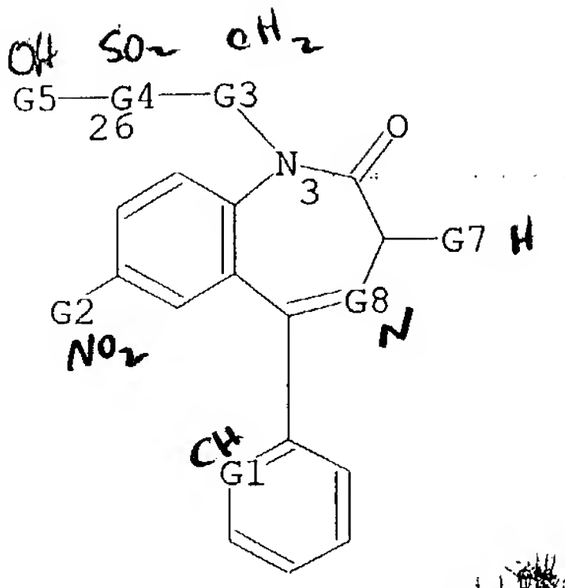
GI



I

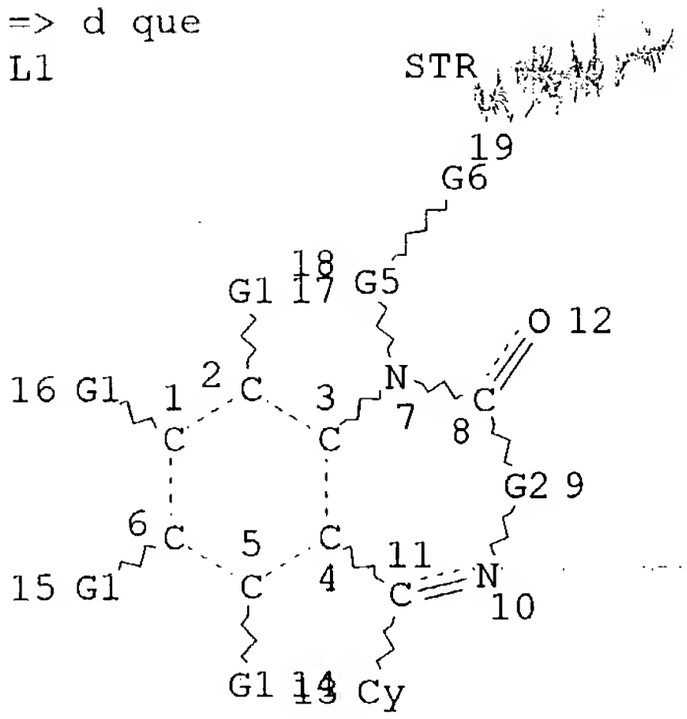
AB Benzodiazepine derivs. I [X = CH, N, C-halogen; R1 = H, Me, RZQ; R2 = H, OH; R3 = O or nonbonding electron pair; R4 = RZQ when R1 = H, Me or R4 = halogen, NO2, NH2, NHCOMe when R1 = RZQ; R = linking group containing 0-20 C and heteroatoms (≤12) arranged in a straight or branched chain and containing ≤2 rings and ≤4 heteroatoms and ≤2 S or N or 1 O may be linked in sequence; Z = CO, CNH, NH, NMe, N2, SO2, CH2; Q = H, OH, halogen, acyloxy, N-succinimidyloxy, N-phthalimidyloxy, alkoxy, (substituted) phenoxy, N-imidazolyl, 1-benzotriazolyloxy, poly(amino acid) (derivative), immunogenic carrier, or amino, amido, anidino, (thio) urea, (thio) carbamate, triazinylamino, or (carboxyamino)-sulfonamido derivative of fluorescein] are prepared as precursors, immunogens, or tracers for a fluorescence-polarization immunoassay for determining the presence or amount of benzodiazepines and their metabolites in a sample. An immunogen was prepared by coupling 1-carboxymethyl-7-chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one with bovine serum albumin via dicyclohexylcarbodiimide and N-hydroxysuccinimide.

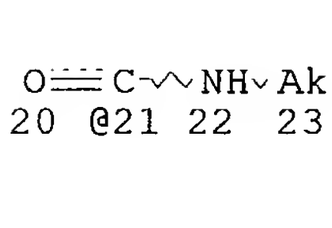
MSTR 1E

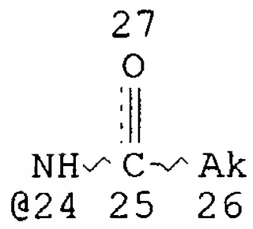


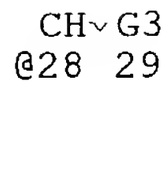
G1 = CH
G2 = NO2
G3 = CH2
G4 = SO2
G5 = OH
G8 = N
MPL: claim 1

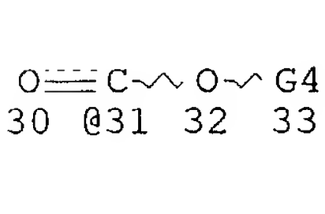
=> d que
L1 STR

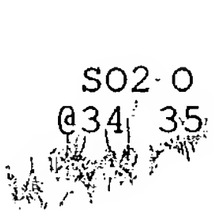


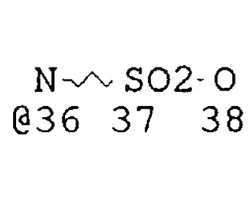


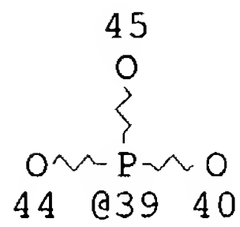












46

Page 1-A

Page 2-A

VAR G1=H/X/NO2/NH2/21/24
VAR G2=CH2/28
VAR G3=AK/OH/31
VAR G4=H/AK
REP G5=(0-20) A
VAR G6=34/36/39/41
NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
GGCAT IS UNS AT 13
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 47

STEREO ATTRIBUTES: NONE

L5 0 SEA FILE=BEILSTEIN SSS FUL L1